said primers, said probes being selected from the group consisting of at least 15-25 contiguous nucleotides of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, which distinguishes said species, each said labeled probe being specific for one of said fungal species from said group, to determine whether said fungal species identified by each said labeled probe is present in said sample.

Remarks

The July 25, 2002 Official Action and references cited therein have been carefully reviewed. Claims 2-5 and 20-22 are currently pending and under consideration. In light of the claim amendments, evidence and following remarks, favorable reconsideration and allowance of the application are respectfully requested.

At the outset, it is noted that although the Examiner indicates that no claims are allowed, claim 22 has not been rejected under any grounds and thus is presumably directed to allowable subject matter. The Examiner is respectfully requested to issue another action to clarify this point. Additionally, the Examiner correctly presumes that the subject matter of the various claims was commonly owned at the time any invention covered therein was made.

The Examiner has instituted new grounds of rejection allegedly necessitated by the claim amendments presented in Applicant's last response.

Claims 2-4, and claim 20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, pages 315-322, 1990) and Beck, US Patent 5,827,695, in view of Borsuk et al. (Acta Biochimica Polionica, Vol. 41:73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. 44:225-230, 1998) and Pazoutova (GenBank Accession No. AJ001331 (August 1997) and

Peterson (GenBank Accession No. U65306 (May 1997) and Aguirre et al. (GenBank Accession No. U93683 (May 1997) and further in view of Sandhu et al. US Patent 5,707,802.

The Examiner has maintained the rejection of claim 5 under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. and Beck in view of Borsuk et al. and Nikkuni et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Nelson et al., US Patent 5,827,656.

At page 12 of the Official Action, the Examiner has rejected claim 21 under 35 U.S.C. §103(a) as allegedly being unpatentable over White et al. and Beck et al. in view of Borsuk et al. and Nikkuni et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Sandhu et al. and Wang et al., US Patent 5,876,977.

Finally, the Examiner has rejected claim 21 under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. and Beck in view of Borsuk et al. and Nikkuni et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Sandhu et al. and in further view of Felgner et al., US Patent 6,165,720.

The rejections summarized above constitute the entirety of the issues raised by the Examiner in the July 25, 2002 Official Action.

CLAIMS 2-4 AND 20 ARE NOT RENDERED OBVIOUS BY THE PRIOR ART CITED BY THE EXAMINER

Claims 2-4, and claim 20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, pages 315-322, 1990) and Beck, US Patent 5,827,695, in view of Borsuk et al. (Acta Biochimica Polionica, Vol. 41:73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. 44:225-230, 1998) and Pazoutova (GenBank Accession No. AJ001331 (August 1997) and Peterson (GenBank Accession No. U65306 (May 1997) and Aguirre et al. (GenBank Accession No. U93683 (May 1997) and further in

view of Sandhu et al. US Patent 5,707,802.

A summary of the arguments currently under dispute is appropriate at this point. Briefly, it is the Examiner's contention that White et al. teach that the ITS1 and IST5 primers are located within the small rDNA and the ITS4 primer is located in the large rDNA and using primer sets from these respective regions should facilitate amplification of both the ITS1 and ITS2 regions which are highly variable among fungal species. The Examiner further asserts that Beck teaches methods for cloning ITS DNA sequences, and further that the general isolation of DNA from fungal isolates is known in the art. The Examiner acknowledges that neither White et al. nor Beck teach SEQ ID NO:2. Applicants note that Beck is directed to an analysis of fungal pathogens of wheat rather than medically important Aspergillus species.

The Examiner states that Borsuk et al. show alignments of ITS1 and ITS2 regions of three Aspergillus species. Applicants note that Borsuk et al. also do not teach an isolated primer consisting of SEQ ID NO:2. The Examiner relies on Nikkuni et al. for the teaching that ITS regions may be used to distinguish between strains of fungi. The Examiner cites Peterson et al. and Aguirre et al. for teaching Aspergillus sequences from *Aspergillus terreus*, *Aspergillus niger*, and *Aspergillus fumigatus* respectively. Each of these sequences contains the sequence of SEQ ID NO:2 as part of a larger sequence, but none of the cited prior art references disclose a primer consisting of SEQ ID NO:2.

According to the Examiner it would have been *prima facie* obvious to one of ordinary skill in the art to modify the teachings of White and Beck, given the specific sequences for Aspergillus as taught by Borsuk, Nikkuni, Pazuotova, Peterson, and Aguirre.

The Examiner states that the combination of references suggests that ITS primers can be used to distinguish species, and that any primer from a conserved region would be expected

to function in the instant method. The Examiner contends that SEQ ID NO:2 and the ITS4 primer of White et al. are functional equivalents, for use in the amplification of ITS1 and ITS 2 regions of Aspergillus. The Examiner relies on Beck for the suggestion to design primers to conserved regions and thereby identify genus specific primers. The Examiner concludes that while the claimed primer set may be unique, methods for use of the same in amplification methods to differentiate different Aspergillus species is obvious over the prior art. The Examiner also argues it would be obvious to detect Aspergillus in a patient sample because it is well known that the Aspergillus fungi are linked to disease.

Applicants respectfully traverse this rejection. At the outset, it is noted that all of the claims require a primer set consisting of SEQ ID NO:1 and SEQ ID NO:2, which is capable of amplifying *Aspergillus ustus (SEQ ID NO:3), Aspergillus terreus (SEQ ID NO:4), Aspergillus niger (SEQ ID NO:5), Aspergillus fumigatus (SEQ ID NO:6), Aspergillus flavus (SEQ ID NO:7),* and *Aspergillus nidulans (SEQ ID NO:8).* Applicants note that the Examiner has never addressed this recitation of amplified sequences from specific strains of *Aspergillus* in her rejection of the present claims.

None of the references, alone or combined, teach detection of specific *Aspergillus* species by amplifying a fragment using a primer set comprising SEQ ID NO:1 and SEQ ID NO:2, and further, none of the references cited by the Examiner teach, or render this primer set obvious.

First, it is noted that although SEQ ID NO:2 is isolated from the 28s conserved region, the teaching of one primer from the 28s region does not render all other primers from that region obvious. This is because for a genus to render a species obvious, the art must teach motivation to select that particular species. In this case, absent the hindsight provided by applicant's own disclosure, there is no motivation to select a primer consisting of SEQ ID NO:2.

MPEP 2144.08 4a states that-

> "Some motivation to select the claimed species or subgenus must be taught in the prior art. See e.g., Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ('No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.')"

Further, at the end of this MPEP section, the conclusion states that

> "explicit findings on motivation or suggestion to select the claimed invention should also be articulated in order to support a 35 U.S.C. 103 ground of rejection...Conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute factual findings."

Thus there is no motivation to select the instant primer set for bracketing a hypervariable region (the primers of SEQ ID NO:1 and SEQ ID NO:2) which is instantly claimed.

Second, as set forth above, the references alone, or combined are silent as to a polynucleotide consisting of SEQ ID NO:2. It is a well-settled premise in patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966)

Contrary to the Examiner's allegation, the selection of a specific primer comprising SEQ ID NO:2 is not obvious in view of the disclosure of the ITS4 primer of White et al. At page 8 of the Official Action, the Examiner states that no evidence has been presented to indicate that the selection of the primers was other than routine. In response to this assertion by the Examiner, Applicants hereby submit a Declaration by Dr. Peter Iwen for consideration by the Examiner.

DIRECT AND INDIRECT COMPARATIVE TESTS ARE PROBATIVE OF NONOBVIOUSNESS

"Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the

closest prior art which is commensurate in scope with the claims." In re Boesch, 617 F2.d 272, 205 USPQ 215 (CCPA 1980)

The Declaration of Dr. Peter Iwen provides comparative evidence which demonstrates that in contrast to the primer set instantly claimed, the primer set of White et al. is not capable of amplifying *A. terreus,* only weakly amplifies *A. flavus,* and *A. nidulans* and thus is not **functionally equivalent** to the primer set of the present invention.

Because the White et al. reference alone or in combination with the other references relied on by the Examiner neither describes essential elements of the instant claims, nor places the invention as presently claimed in the hands of the public, a prima facie case of obvious has not been established. Accordingly, the rejection of claims 2-4 and 20 under 35 U.S.C. §103(a) is improper and should be withdrawn.

THE PRIOR ART RELIED ON BY THE EXAMINER FAILS TO RENDER TE SUBJECT MATTER OF CLAIM 5 OBVIOUS

The Examiner has maintained the rejection of claim 5 under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. and Beck in view of Borsuk et al. and Nikkuni et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Nelson et al., US Patent 5,827,656.

The Examiner states that neither White, Beck, Borsuk, Nikkuni, Pazoutova, Peterson, nor Aguirre, teach detection of more than one probe using either different signal moieties or separation moieties, but that Nelson teaches a method for assaying a plurality of nucleic acid analytes suspected of being in a sample by providing a plurality of probes with different labels and detecting, and that this method allows simultaneous detection and quantification of more than one specific nucleic acid in a sample.

Applicants respectfully traverse this grounds of rejection. Nelson et al. does not teach an isolated primer set comprising SEQ ID NO:1 and SEQ ID NO:2, or using labeled probes selected from the group consisting of 15-25 contiguous nucleotides of SEQ ID NO:3-8 to identify specific *Aspergillus* species. Thus Nelson et al. fails to correct the deficiencies of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, and Aguirre, as set forth above.

Accordingly, Applicants respectfully submit that the §103 rejection of claim 5 is likewise improper and should be withdrawn.

CLAIM 21 IS NOT OBVIOUS OVER WHITE ET AL. AND BECK, IN VIEW OF BORSUK ET AL. AND NIKKUNI ET AL. AND PAZOUTOVA AND PETERSON AND AGUIRRE ET AL. AND FURTHER IN VIEW OF SANDHU ET AL. AND FURTHER IN VIEW OF WANG ET AL.

The Examiner has rejected claim 21 under 35 U.S.C. §103(a) as allegedly being unpatentable over White et al. and Beck et al. in view of Borsuk et al. and Nikkuni et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Sandhu et al. and Wang et al., US Patent 5,876,977.

The Examiner states that neither White, Beck, Borsuk, Nikkuni, Pazoutova, Peterson, Aguirre, nor Sandhu teach detection of fungal nucleic acids by restriction mapping, but that Wang teaches identification of ITS regions by amplifying and detecting discrete and species specific RFLP patterns and that these methods are reliable, are highly sensitive, have easily interpreted results, and provide a definitive way to identify similar nucleic acids.

Applicants respectfully traverse this grounds of rejection. Wang et al. does not teach an isolated primer set comprising SEQ ID NO:1 and SEQ ID NO:2, or using labeled probes selected from the group consisting of 15-25 contiguous nucleotides of SEQ ID NO:3-8 to identify specific *Aspergillus* Inasmuch as Wang et al. fail to correct the deficiencies of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson,

Aguirre, and Sandhu for all of the reasons and evidence set forth above, Applicants respectfully request that the rejection of claim 21 be withdrawn.

CLAIM 21 IS ALSO NOT RENDERED OBVIOUS BY THE PRIOR ART CITED BY THE EXAMINER

The Examiner has rejected claim 21 under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. and Beck in view of Borsuk et al. and Nikkunie et al. and Pazoutova and Peterson and Aguirre et al. and further in view of Sandhu et al. and in further view of Felgner et al., US Patent 6,165,720.

The Examiner states that neither White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre, nor Sandhu teach detection of nucleic acids by fluorescent molecular probes, but Felgner teaches FISH (Fluorescent In Situ Hybridization) which allows in situ detection.

Applicants respectfully traverse this grounds of rejection. Felgner et al. does not teach an isolated primer set comprising SEQ ID NO:1 and SEQ ID NO:2, or using labeled probes selected from the group consisting of 15-25 contiguous nucleotides of SEQ ID NO:3-8 to identify specific *Aspergillus* species. Like Nelson et al, and Wang et al., Felgner et al. fail to correct the deficiencies of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre, and Sandhu set forth above. Accordingly, Applicants request that this rejection of claim 21 be withdrawn.

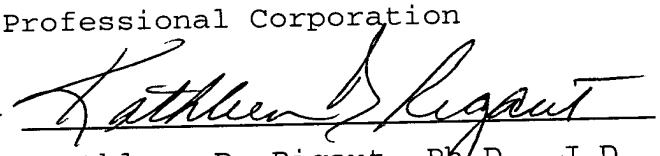
CONCLUSION

It is respectfully requested that the Declaration and claim amendments presented herewith be entered in this application, since the Declaration merely provides experimental evidence demonstrating the superior qualities of the instantly claimed primer set and the amendments are

primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In view of the present claim amendments, and the foregoing remarks, it is respectfully urged that the rejections set forth in the July 25, 2002 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 

Kathleen D. Rigaut, Ph.D., J.D.
PTO Registration No. 43,047

Telephone: (215) 563-4100
Enclosures: Declaration by Dr. Peter Iwen
Exhibit A

Appendix A

Marked Up Copy of Claims

2. (Twice Amended) A method of determining whether one or more fungal *Aspergillus* species [selected from the group consisting of *Aspergillus ustus (SEQ ID NO:3), Aspergillus terreus (SEQ ID NO:4), Aspergillus niger (SEQ ID NO:5), Aspergillus fumigatus (SEQ ID NO:6), Aspergillus flavus (SEQ ID NO:7),* and *Aspergillus nidulans (SEQ ID NO:8),*] is present in a sample, said method comprising the following steps:

a) extracting nucleic acid material from fungi contained in a patient sample from a patient suspected of having an *Aspergillus* infection;

b) adding two oligonucleotide primers, one of said primers consisting of SEQ ID NO:1 and the other primer consisting of SEQ ID NO:2, said primers bracketing a hypervariable region on the rRNA present in the fungal species of said group, and said primers being capable of amplifying *Aspergillus ustus (SEQ ID NO:3), Aspergillus terreus (SEQ ID NO:4) Aspergillus niger (SEQ ID NO:5), Aspergillus fumigatus (SEQ ID NO:6), Aspergillus flavus (SEQ ID NO:7),* and *Aspergillus nidulans (SEQ ID NO:8);*

c) amplifying the sequence between said primers; and

d) using one or more detectably labeled probes directed to a portion of the hypervariable region bracketed by said primers, said probes being selected from the group consisting of at least 15-25 contiguous nucleotides of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, which distinguishes said species, each said labeled probe being specific for one of said fungal species from said group, to determine whether said fungal species identified by each said labeled probe is present in said sample.

Iwen, Henry, and Hinrichs
U.S. Patent Application No. 09/580,797

Primer Comparison 1